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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/698,781	10/27/2000	Rene S. Hubert	G&C 129.23-US-U1	6670

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/698,781	HUBERT ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *58, 59, 62, and 63* is/are allowed.

6)☒ Claim(s) *60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed November 6, 2003 is acknowledged and has been entered. Claims 39-57 have been canceled. Claims 58-63 have been added.

2. Claims 58-63 are pending in the application and are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

3. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed May 6, 2003 have been withdrawn.

Claim Objections

4. Claims 60 and 61 are objected to because the claims recite, "a polypeptide of nine or ten amino acids in length". The claims would more properly read, "a peptide of nine or ten amino acids". Additionally, claims 60 and 61 are objected to because the claims recite, "whereby said polypeptide binds to an HLA class I molecule". The claims are not drawn to a method and do not recite any active step by which said polypeptide would be expected to bind an HLA class I molecule.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The specification describes the polynucleotide sequence of SEQ ID NO: 3, which encodes the amino acid sequence of SEQ ID NO: 3. In addition, at page 55, for example, the specification describes some peptides, which have amino acid sequences that are fragments of the amino acid sequence set forth as SEQ ID NO: 2, which peptides bind to an HLA class I molecule, i.e., HLA-A2.

However, the claims presently encompass a much broader genus of nucleic acid molecules, which are fragments of the nucleic acid molecule of SEQ ID NO: 3, which encode a peptide of nine or ten amino acids, which bind to an HLA class I molecule. The peptide encoded by the members of the claimed genus of nucleic acid molecules does not necessarily have an amino acid sequence, which is a fragment of the amino acid sequence of SEQ ID NO: 3. Many of the peptides of nine or ten amino acids, which are expected to bind to an HLA class I molecule, which are encoded by nucleic acid molecules encompassed by the claims, are encoded by one of the two alternative reading frames of the polynucleotide sequence set forth as SEQ ID NO: 2. The specification fails to describe the amino acid sequences of the peptides encoded by

members of the claimed genus of nucleic acid molecules, which do not have amino acid sequences, which are fragments of SEQ ID NO: 3.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of apparently unrelated species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicants were in possession of the claimed genus. Factual evidence of an actual reduction to practice has not been disclosed by Applicants in the specification; nor have Applicants shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor have Applicants described distinguishing identifying characteristics sufficient to show that Applicants were in possession of the claimed invention at the time the application was filed.

In addition, the peptides described in the specification are not deemed representative of the whole of the peptides encoded by the members of the claimed genus of nucleic acid molecules, which peptides have amino acid sequence that are fragments of SEQ ID NO: 3, as the specification fails to teach a distinguishing feature, which is common among at least a substantial number of the peptides encoded by the claimed genus. Unless distinguishing characteristics common to at least a substantial number of the members of the genus of proteins encoded by the claimed nucleic acid molecules is explicitly recited in the claims, which would enable the skilled artisan to instantly recognize at least a substantial number of the members of the genus, or to

readily distinguish members of the claimed genus from all others, the written description requirement set forth under 35 USC § 112, first paragraph has not been met.

Although the members of the claimed genus of nucleic acid molecules are described as encoding a peptide, which binds to an HLA class I molecule, this function of the peptides is not correlated with any particular structural feature of the peptides. Absent the disclosure of such a structure-function relationship, describing the peptides as capable of binding HLA-A2, for example, does not describe the structure of the peptides, nor does it describe the structures of the claimed nucleic acid molecules encoding those peptides; it describes what the peptide must do, not what the peptides are.

In addition, Shastri et al. (*Annual Review of Immunology* 20: 463-493, 2002) teaches the peptides that bind MHC molecules, such as HLA-A2 or any other class I MHC molecule, represent the entire ensemble of polypeptides expressed with a cell. Accordingly, absent any evidence otherwise, it is expected every peptide of about 9 or 10 amino acids, which is a fragment of some protein expressed by a cell, is capable of binding at least one HLA class I molecule. By parallel, absent any evidence otherwise, it is expected that at least one HLA class I molecule binds each and every peptide encoded by the members of the claimed genus of nucleic acid molecules. Consequently, describing the peptides encoded by the members of the claimed genus of nucleic acid molecules does not serve to delineate the claimed genus, or enable the skilled artisan to recognize or distinguish its members from others.

7. Claims 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a fragment of a polynucleotide comprising the polynucleotide sequence set forth in SEQ ID NO: 2 or nucleotides 3-776 of said polynucleotide sequence, which encodes a fragment of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 3 or amino acids 33-258 of said amino acid sequence, which fragment of the polypeptide is capable of eliciting the production of an antibody that binds specifically to the polypeptide of SEQ ID NO: 3 or which fragment of the polynucleotide is capable of specifically hybridizing to a nucleic

acid molecule comprising SEQ ID NO: 2, does not reasonably provide enablement for making or using any fragment of a polynucleotide comprising the polynucleotide sequence set forth in SEQ ID NO: 2 or nucleotides 3-776 of said polynucleotide sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims. Moreover, the amount of guidance, direction, and exemplification set forth in the disclosure would be insufficient to enable the skilled artisan to have a reasonable expectation of successfully making and using the claimed invention without having the need to perform an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims presently encompass a genus of nucleic acid molecules, which are fragments of the nucleic acid molecule of SEQ ID NO: 2, which encode a peptide of nine or ten amino acids, which bind to an HLA class I molecule. Many of the peptides of nine or ten amino acids, which are expected to bind to an HLA class I molecule, which are encoded by nucleic acid molecules encompassed by the claims, are encoded by one of the two alternative reading frames of the polynucleotide sequence set forth as SEQ ID NO: 2. The specification teaches the peptides encoded by the claimed nucleic acid molecules can be used to produce an antibody that binds to the peptide, but the specification fails to describe the proteins to which the antibodies produced by the vast majority of members of the claimed genus of nucleic acid molecules bind. Therefore, the skilled artisan would not know how to use the peptide or the antibody; and the

specification would merely provide an invitation to the skilled artisan elaborate a use for the claimed invention, which elaboration would require the skilled artisan to perform an undue amount of experimentation.

Although any member of the genus of claimed nucleic acid molecules is capable of hybridizing to a nucleic acid molecule comprising the polynucleotide sequence set forth as SEQ ID NO: 2, only those members of the genus, which hybridize selectively to the nucleic acid molecule of SEQ ID NO: 2 can be used as a probe to determine the presence, or measure the amount of the nucleic acid molecule. The specification only provides adequate guidance and direction to use those members of the claimed genus, which are capable of selectively hybridizing to the nucleic acid molecule of SEQ ID NO: 2. The specification fails to provide adequate guidance and direction to use the members of claimed genus, which are incapable of selectively hybridizing to the nucleic acid molecule of SEQ ID NO: 2, because the specification fails to teach methods for using the other polynucleotide sequences to which the claimed nucleic acid molecule bind. As established by the previous Office action, the skilled artisan would not accept the assertion that any polynucleotide sequence to which one of the claimed nucleic acid molecules binds, except the polynucleotide sequence set forth in SEQ ID NO: 2, would encode a polypeptide that has a biological activity that is identical or even similar to the protein comprising SEQ ID NO: 3. Therefore, the skilled artisan would not know how to use polynucleotide sequences other than SEQ ID NO: 2 and could not therefore use members of the claimed genus of nucleic acid molecules, which do not bind selectively to a nucleic acid molecule comprising SEQ ID NO: 2. Again, with the exception of members of the claimed genus of nucleic acid molecules, which selectively hybridize to the nucleic acid molecule of SEQ ID NO: 2, the specification would merely provide an invitation to the skilled artisan elaborate a use for the claimed invention, which elaboration would require the skilled artisan to perform an undue amount of experimentation.

Although the members of the claimed genus of nucleic acid molecule encode a peptide, which binds to an HLA class I molecule, the fact that the peptide binds an HLA class I molecule, e.g., HLA-A2, does not render the peptide useful. Again, many of the

peptides of nine or ten amino acids, which are expected to bind to an HLA class I molecule, which are encoded by nucleic acid molecules encompassed by the claims, are encoded by one of the two alternative reading frames of the polynucleotide sequence set forth as SEQ ID NO: 2. Thus, many of the peptides are epitopes of proteins, which have not been described in the specification. Therefore, although the peptide might be used to stimulate a class I-restricted immune response, because it is unknown to which protein the immune response would be generated, unless the immune response is generated against the polypeptide of SEQ ID NO: 3, the skilled artisan would not know how to use the peptide.

Even if the peptide stimulates a class I-restricted immune response against the protein of SEQ ID NO: 3, i.e., binds to an HLA-A2 molecule of immune effector cell, the skilled artisan could not use the claimed invention without need of having to perform an undue amount of experimentation. At page 55, for example, the specification teaches the peptide capable of stimulating a class I-restricted immune response against the protein of SEQ ID NO: 3, or which binds HLA-A2 can be used as a cancer vaccine. However, the art of cancer immunotherapy is highly unpredictable and in the absense of exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that the claimed invention can be used effectively to treat an individual diagnosed with cancer.

Bodey et al. (*Anticancer Research* **20**: 2665-2676, 2000) teach, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey et al. comment, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). Thus, little has changed to alter the artisans' expectations of the still prospective immunotherapy since the invention was made. Cox et al. (*Science* **264**: 716-719, 1994) teach, "neither adoptive transfer of melanoma-specific CTLs nor specific active immunotherapy with whole melanoma cells or cell-derived preparations has led to the eradication of melanoma in more than a minority of patients" (page 716, column 2). Then again, even

that small note of promise has since faded. Bodey et al. disclose, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (apge 2668, column 2). In the abstract Bodey et al. speculate upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research* **7**: 46-49, 1995) states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell et al. further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). More recently, Bodey et al. (cited supra) state, "there should be caution about assuming that a single epitope or even a few epitopes combined will be as effective 'crude' materials, which might better be thought of as 'polyvalent'" (page 2668, column 2). Spitler (*Cancer Biotherapy* **10**: 1-3, 1995) recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director

of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Furthermore, with regard to anticancer drug discovery, Gura (*Science* **278**: 1041-1042, 1997), for example, teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Although the teachings of Bergers et al. (*Current Opinion in Genetics and Development* **10**: 120-127, 2000) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger et al.. Bergers et al. teach, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers et al., disclose that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers et al. also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas.

Thus, one skilled in the art cannot predict the effect of administering a pharmaceutical composition purported to have a desired pharmacological effect to a

subject. Always the efficacy of any unproven drug regimen must be determined empirically. Therefore, in such an unpredictable art as this, the disclosure of such empirical determinations (i.e., working exemplification) must be commensurate in scope with its expected and indicated uses if the specification is to be considered enabling; otherwise, in the absence of sufficient exemplification, the skilled artisan would have to perform undue experimentation to use the claimed invention with a reasonable expectation of success.

Note: Amending claims 60 and 61 to recite the following limitation will obviate this ground of rejection:

"wherein said peptide is capable of eliciting the production of an antibody that binds specifically to the polypeptide of SEQ ID NO: 3 or wherein said polynucleotide fragment is capable of specifically hybridizing to the nucleic acid molecule of SEQ ID NO: 2 or its full complement".

Conclusion

8. Claims 58, 59, 62, and 63 are allowed. Claims 60 and 61 are not allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
February 6, 2004

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